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Dopaminergic 2-Aminotetralins: Affinities for Dopamine D_2-Receptors, Molecular Structures, and Conformational Preferences

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SUMMARY

A combination of X-ray crystallography, NMR spectroscopy, and molecular mechanics (MMP2) calculations was used to determine the three-dimensional structures and conformational preferences of the enantiomers of 5-hydroxy-2-(di-*n*-propylamino)tetralin and their C_1-methylated derivatives. In addition, the affinities of the compounds for striatal ^{3}H-spiroperidol- and ^{3}H-*N*-*n*-propylnorapomorphine-binding sites were determined. In the present series, the dopamine D_2-receptor agonists have the *S*-configuration at the nitrogen-bearing carbon (C_2), whereas the only established D_2-receptor antagonist, 1*S*,2*R*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (1*S*,2*R*-UH-242), has the opposite absolute configuration at C_2. Two conformational parameters, the tetralin inversion angle (ϕ) and the dihedral angle τ(C_1, C_2, N, N-H or electron pair) (τ_N), are shown to be critical for D_2-receptor agonism; ϕ values around 0° and τ_N values around 60° appear to be optimal. The low D_2-affinity of 1*S*,2*S*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin seems to be related to its inability to assume a low-energy "D_2-receptor agonistic conformation." It is noted that the common structural denominator between the D_2-receptor antagonists 1*S*,2*R*-UH-242 and 6a*S*-apomorphine is their inability to assume "dopamine D_2-receptor agonistic nitrogen electron pair orientations."

Structure-activity relationship studies of dopaminergic 2-aminotetralin derivatives have attracted considerable interest during the last decade. Results obtained have been used in discussions of optimal N-substitution, C_2-configuration, and aromatic substitution pattern for DA receptor activation, and a number of hypothetic DA receptor models have emerged from attempts to rationalize available data (for reviews, see, for example, Refs. 1 and 2). Additional information may be obtained by variation of parameters other than those already studied. For example, introduction of methyl substituents in the non-aromatic ring of the bicyclic 2-aminotetralin moiety would make it possible to map previously undefined parts of the DA receptors. Therefore, some C_1-methyl-substituted derivatives of the potent DA receptor agonist 5-OH DPAT (3) were prepared (Fig. 1) (4–6). Unexpected results were obtained when these compounds were investigated pharmacologically by use of behavioral and biochemical assays in rats (4–7); the (−)-enantiomer of AJ-116 appeared to have a pharmacological profile similar to that of the classical DA receptor agonist, 6a*R*-APO, whereas the diastereomeric (−)-UH-242 seemed to activate preferentially DA autoreceptors. Both compounds were considerably lower in potency than the C_1-unsubstituted (−)-5-OH DPAT. The low potency of the (−)-enantiomer of AJ-116 was surprising when considering the high dopaminergic potency of the rigid analogue, 4a*S*,10b*S*-*trans*-OHBQ (8). The (+)-enantiomer of UH-242 was classified as an *antagonist* with preferential action on DA-autoreceptors, whereas (+)-AJ-116 and (±)-UH-148 appeared to be inactive (4–6). Also, (+)-5-OH DPAT, which has been assigned the *R*-configuration on the basis of X-ray crystallography (9) and chemical correlation (10), seems to possess little, if any, dopaminergic activity (3, 8, 11–13).

In the present study we have used a combination of X-ray

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ABBREVIATIONS: DA, dopamine; 2*S*- and 2*R*-5-OH DPAT, 2*S*- and 2*R*-5-hydroxy-2-(di-*n*-propylamino)tetralin; 1*S*,2*R*- and 1*R*,2*S*-UH-242, 1*S*,2*R*- and 1*R*,2*S*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin; 1*S*,2*S*- and 1*R*,2*R*-AJ-116, 1*S*,2*S*- and 1*R*,2*R*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin; UH-148, 5-hydroxy-1,1-dimethyl-2-(di-*n*-propylamino)tetralin; 6a*S*- and 6a*R*-APO, 6a*S*- and 6a*R*-apomorphine; NPA, *N*-*n*-propylnorapomorphine; 4a*S*,10b*S*-*trans*-OHBQ, 4a*S*,10b*S*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline; 4a*S*,10b*R*-*cis*-OHBQ, 4a*S*,10b*R*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline; EDTA, ethylenediaminetetraacetic acid; DOPA, 3,4-dihydroxyphenylalanine.

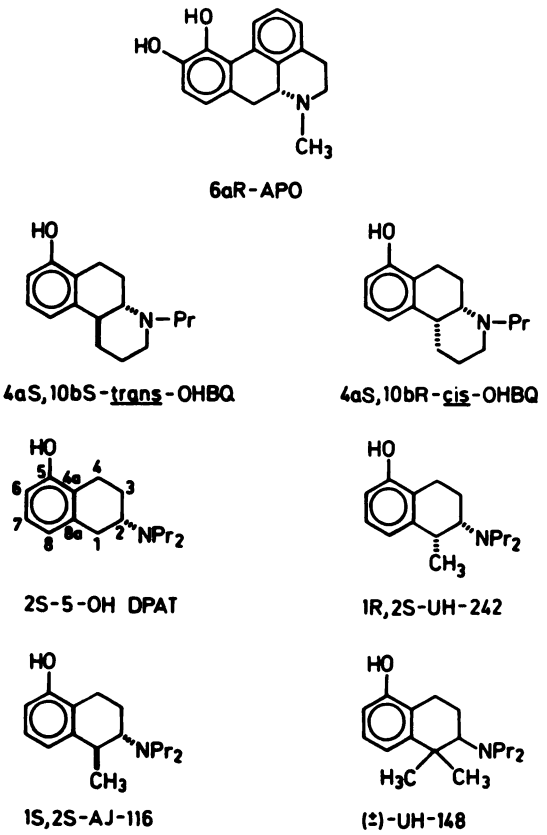


Fig. 1. Chemical structures of the DA receptor agonists 6a*R*-APO and 4a*S*,10b*S*-*trans*-OHBQ, the inactive 4a*S*,10b*R*-*cis*-OHBQ, and four 5-hydroxy-2-(di-*n*-propylamino)tetralins. *Pr*, *n*-propyl.

crystallography, NMR spectroscopy, and empiric force field calculations to elucidate the three-dimensional structures and conformational preferences of the enantiomers of 5-OH DPAT and their C_1-methylated analogues; X-ray crystallography established the molecular structures and absolute configurations of (−)-AJ-116 hydrochloride and (+)-UH-242 hydrobromide. Molecular mechanics (MMP2) calculations resulted in the identification of several low-energy conformations for each of the compounds investigated. Finally, the conformational preferences in solution (methanol-d_4) were investigated by use of 400-MHz ^{1}H-NMR spectroscopy. In addition, the affinities of the various 2-aminotetralin derivatives for striatal ^{3}H-spiroperidol and ^{3}H-NPA sites were determined. The information thus obtained has been analyzed qualitatively in terms of structural requirements for DA D_2-receptor agonism and antagonism.

Materials and Methods

The syntheses of 2*R*- and 2*S*-5-OH DPAT, (+)- and (−)-AJ-116, (+)- and (−)-UH-242, and (±)-UH-148 have been reported elsewhere (3–6).

X-Ray Crystallography

Crystal data. *(−)-AJ-116 hydrochloride:* $C_{17}H_{27}NO \cdot HCl$, formula weight 297.87, monoclinic, space group $P2_1$, a = 9.1832(9), b = 9.8054(12), c = 9.6210(7), Å, β = 106.795(7)°, V = 829.37 Å^3, d_{calc} = 1.19 gcm^{-3}, z = 2, μ = 19.9 cm^{-1}.

(+)-UH-242 hydrobromide: $C_{17}H_{27}NO \cdot HBr$, formula weight 342.32, monoclinic, space group $P2_1$, a = 14.229(2), b = 8.022(1), c = 16.858(2), Å, β = 114.06(1)°, V = 1757 Å^3, d_{calc} = 1.29 gcm^{-3}, Z = 4, μ = 34.7 cm^{-1}.

The dimensions of the crystals used in the data collections were 0.24 × 0.15 × 0.05 mm^3 and 0.43 × 0.05 × 0.02 mm^3 for (−)-AJ-116·HCl and (+)-UH-242·HBr, respectively. The angular settings of 25 reflections were measured to calculate the lattice parameters. Intensities were recorded on an Enraf-Nonius CAD4F-11 diffractometer using monochromated Cu$K\alpha$-radiation. For both crystals, reflections within one semisphere of reflection and with $\theta < 60°$ were measured. The $\theta/2\theta$ scan method was used and three standard reflections were checked every 2 hr. At the end of the data collection the intensities of the standard reflections for both crystals had decreased by 5%. The intensities were scaled to account for this decay. In all, 2621 and 5410 reflections were measured for (−)-AJ-116·HCl and (+)-UH-242·HBr, respectively. Of these, 1559 for (−)-AJ-116·HCl and 2847 for (+)-UH-242·HBr, having $I > 3\sigma(I)$ were considered observed. The intensities were corrected for Lorenz and polarization effects but not for extinction or absorption.

Structure solution and refinement. The positions of the halogen atoms were determined from Patterson maps and the remaining non-H atoms were found by using the direct methods program DIRDIF (14). The H atoms of (−)-AJ-116·HCl were all obtained from a difference Fourier map. For (+)-UH-242·HBr, the H atoms connected to C atoms are at calculated positions (except the H atoms of the C_1-methyl group, which were omitted), and the H atoms connected to the N or O atoms were found from a difference Fourier map. Refinement was carried out by the full matrix least squares method using anisotropic temperature factors for the non-H atoms. The coordinates of the H atoms of (−)-AJ-116·HCl as well as their isotropic temperature factors were refined, whereas, for (+)-UH-242·HBr, the H atom coordinates were kept fixed and a common isotropic temperature factor (B = 6.0 Å^2) was used. In order to determine the absolute configurations of the two compounds, anomalous dispersion factors (15) were introduced for the non-hydrogen atoms and the two enantiomers of each compound were subsequently refined. Two sets of unique reflections were used in the refinement (*hkl*,*h*-*kl*), and non-observed reflections were allowed to contribute when $F_{calc} > F_{obs}$. When the refinement for (−)-AJ-116·HCl was finished, the residuals for the 1*S*,2*S*- and 1*R*,2*R*-enantiomer were 0.051 and 0.063, respectively [$R(1S,2S)_w$ = 0.055 and $R(1R,2R)_w$ = 0.066]. Corresponding residuals for the 1*S*,2*R*- and 1*R*,2*S*-enantiomers of (+)-UH-242·HBr were 0.047 and 0.053, respectively [$R(1S,2R)_w$ = 0.065 and $R(1R,2S)_w$ = 0.072]. Using Hamilton's test (16), the ratios $R(1R,2R)_w/R(1S,2S)_w$ for (−)-AJ-116·HCl and $R(1R,2S)_w/R(1S,2R)_w$ for (+)-UH-242·HBr are sufficiently great to reject the 1*R*,2*R*- and 1*R*,2*S*-enantiomers, respectively, at the 0.005 significance level. The weighting scheme used in the later part of the refinement was $w = 1/[(1+|F_{obs} - A|/B)^2]$, where A = 8 and B = 7 for (−)-AJ-116·HCl and A = 25 and B = 15 for (+)-UH-242·HBr. The form factors used were those given by Cromer and Mann (17). All calculations were performed on a DEC system 10 computer using mainly the X-ray 72 program system (18).

NMR Spectroscopy

^{1}H- and ^{13}C-NMR spectra were recorded at 400 MHz and 22.5 MHz on JEOL GX-400 and FX-90Q spectrometers, respectively, using 0.1 M CD_3-OD solutions of the hydrochlorides at 25°. Chemical shifts were measured relative to internal tetramethylsilane. Assignments were verified by spin-decoupling experiments. Apparent coupling constants were measured from expanded (1–2 Hz/cm) spectra and refined by use of the JEOL FASNO 5 NMR spectrum simulation program.

Definition of Conformational Parameters

The construction of a tetralin inversion wheel (see Fig. 2) enables one to define the conformation of the non-aromatic ring of any tetralin derivative by use of the tetralin inversion angle, ϕ (19). It should be noted that ϕ is configuration dependent, that is, 2*S*-2-aminotetralin in an ideal halfchair conformation with a pseudoequatorial amino group corresponds to $\phi = 0°$, whereas the enantiomeric conformation in 2*R*-2-aminotetralin corresponds to $\phi = 180°$. The torsion angle $\tau_N = \tau(C_1, C_2, N, H,$ or electron pair) defines the relative direction of the N-H

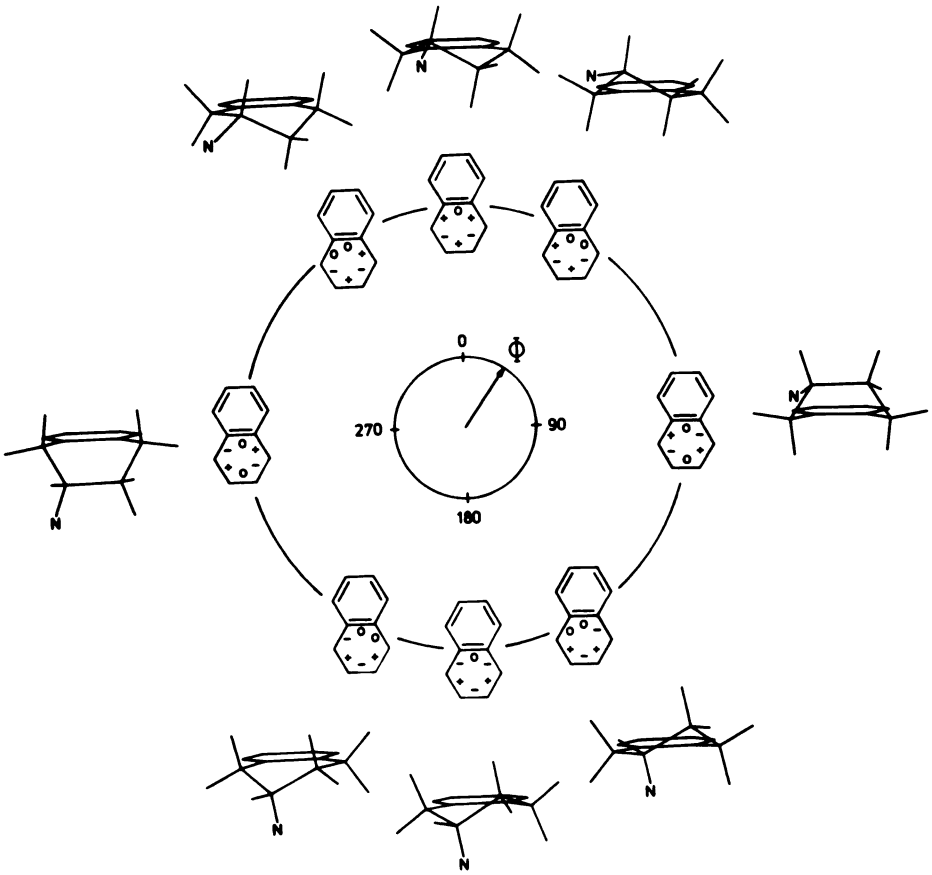


Fig. 2. Tetralin inversion wheel which defines the relationship between tetralin ring conformation and the tetralin inversion angle ϕ. The eight inserted tetralin structures correspond to conformations with $\phi = 0°, 30°, 90°, 150°, 180°, 210°, 270°$, and $330°$, respectively. Each of the tetralin conformations is characterized by the signs (inserted) of the relevant torsion angles. Perspective drawings of eight conformations of a 2*S*-2-aminotetralin moiety are shown outside the corresponding tetralin conformations. It should be noted that, for 2*R*-2-amino-tetralin, a half chair conformation with a pseudoequatorial amino group corresponds to $\phi = 180°$.

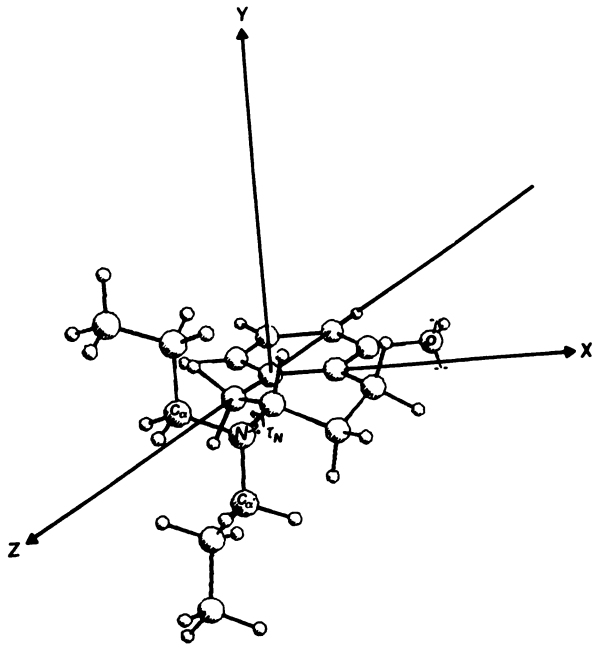


Fig. 3. Coordinate system used in computer-aided structural comparisons and definitions of τ_N, C_α, and $C_{\alpha'}$. The *z* axis of the coordinate system bisects the C_5-hydrogen, C_5, C_{8a}, and C_1; the *x* axis bisects C_{8a} and C_{4a}, and the *y* axis bisects C_{8a}. Shown are τ_N, which is defined as $\tau(C_1, C_2, N, N\text{-}H$, or N-electron pair), C_α, which is defined as the carbon which, in a clockwise sense, is next to the N-H bond (or N-electron lone pair) when viewing along the C_2-N bond, and $C_{\alpha'}$.

bond or the N-electron pair and, indirectly, the direction of the N-C_α and N-C_α'-bonds (compare Fig. 3).

Molecular Mechanics Calculations

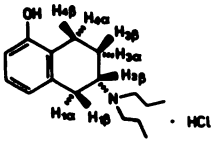
To identify 2-aminotetralin conformations with energies less than 2.5 kcal/mol above the respective global minimum, we applied a strategy which has been described in detail elsewhere (19). For the calculations we utilized the MMP2 program developed by Allinger, modified as previously described (19). Throughout, full energy minimization with respect to all internal coordinates was performed. All calculations were performed on the free bases, and the starting geometry of the hydroxyl group was always set at $\tau(C_{4a}, C_5, O, H) = 180°$.[1] The structural modelling was performed by use of the interactive computer graphics program, MIMIC (methods for interactive modelling in chemistry) (20). Calculations were performed on a VAX 11/780 computer. Computational times ranged from 1 to 20 min/minimization.

^{3}H-Spiroperidol and ^{3}H-NPA Binding

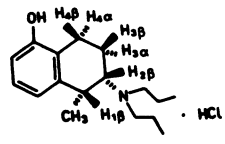
Membrane preparation. Striatal tissue was obtained from male Wistar rats (150–200 g, CDL Groningen) and homogenized in 20 volumes of ice-cold 0.25 M sucrose/1 mM EDTA using an Ultraturrax (1400 rpm, 20 sec). The homogenate was centrifuged twice at 5000 × *g* for 10 min. The supernatants were collected and centrifuged at 43,000 × *g* for 20 min, the pellet was resuspended in 20 volumes of an ice-cold 15 mM Tris-HCl/1 mM EDTA, buffer, pH 7.4 (with 0.01% ascorbic acid for the ^{3}H-NPA assay) and centrifuged at 43,000 × *g* for 20 min. For the ^{3}H-NPA binding, the pellet was resuspended in the buffer and preincubated for 30 min at 37°, centrifuged, resuspended, and centrifuged (43,000 × *g*, 20 min) a last time.

[1] Test calculations have shown that conformations with $\tau(C_{4a}, C_5, O, H)$ around 0° consistently have energies 0.2–0.4 kcal/mol above those of the corresponding conformations with $\tau(C_{4a}, C_5, O, H)$ around 180°.

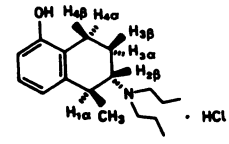
	$H_{1\alpha}$	$H_{1\beta}$	$H_{2\beta}$	$H_{3\alpha}$	$H_{3\beta}$	$H_{4\alpha}$	$H_{4\beta}$
$H_{1\alpha}$	a		9.3				
$H_{1\beta}$		a	4.5				
$H_{2\beta}$			3.69	10.5	2.5		
$H_{3\alpha}$				1.89	-10.5	5.6	10.5
$H_{3\beta}$					2.33	3.0	5.8
$H_{4\alpha}$						a	-16.0
$H_{4\beta}$							2.64



	CH_3	$H_{1\beta}$	$H_{2\beta}$	$H_{3\alpha}$	$H_{3\beta}$	$H_{4\alpha}$	$H_{4\beta}$
CH_3	1.41	7.1					
$H_{1\beta}$		3.41	4.4				
$H_{2\beta}$			3.64	12.7	2.9		
$H_{3\alpha}$				2.06	-12.2	6.5	12.0
$H_{3\beta}$					2.28	1.5	7.1
$H_{4\alpha}$						3.05	-18.0
$H_{4\beta}$							2.69



	CH_3	$H_{1\alpha}$	$H_{2\beta}$	$H_{3\alpha}$	$H_{3\beta}$	$H_{4\alpha}$	$H_{4\beta}$
CH_3	1.37	7.1					
$H_{1\alpha}$		3.23	3.5				
$H_{2\beta}$			3.62	7.2	4.3		
$H_{3\alpha}$				2.04	-14.2	7.6	5.7
$H_{3\beta}$					2.31	5.5	7.5
$H_{4\alpha}$						2.91[b]	-17.3
$H_{4\beta}$							2.66[b]



	CH_3	CH_3	$H_{2\beta}$	$H_{3\alpha}$	$H_{3\beta}$	$H_{4\alpha}$	$H_{4\beta}$
CH_3	1.45						
CH_3		1.51					
$H_{2\beta}$			3.65	10.6	2.6		
$H_{3\alpha}$				2.08	-13.0	5.5	10.9
$H_{3\beta}$					2.30	3.8	6.0
$H_{4\alpha}$						3.05	-17.4
$H_{4\beta}$							2.64

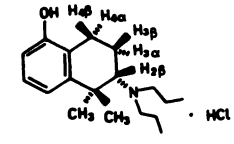


FIG. 4

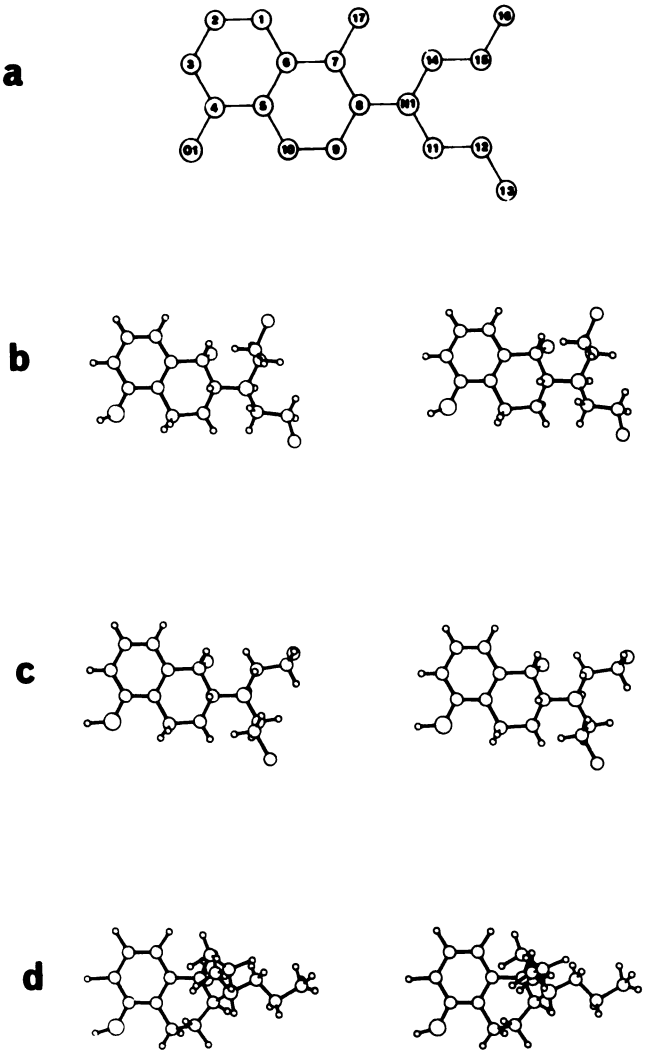


Fig. 5. Atom numbering scheme used in Tables 1 and 2 (*a*) and stereoscopic representations of the solid state (X-ray) conformations of the A- and B-molecules of 1*S*,2*R*-UH-242·HBr (b and c, respectively) and of 1*S*,2*S*,AJ-116·HCl (d). Halogen atoms are not shown. In the representations of 1*S*,2*R*,UH-242·HBr, the C_1-methyl carbon atom lacks hydrogen atoms.

Fig. 4. Selected ^1H NMR spectroscopic data of four 5-hydroxy-2-(di-*n*-propylamino)tetralins in CD_3OD at 25°C (from top to bottom): 5-OH DPAT·HCl, UH-242·HCl, AJ-116·HCl, and UH-148·HCl. Chemical shifts (in ppm) are shown on the diagonals. Proton-proton coupling constants are in Hz. *a*, signals were obscured; *b*, assignments are ambiguous. Observed coupling constants indicate that 5-OH DPAT·HCl, UH-242·HCl, and UH-148·HCl preferentially assume half chair conformations with the dipropylammonium substituents in pseudoequatorial dispositions. In the spectrum of AJ-116·HCl, no large vicinal coupling constants were present. Thus, this compound appears to exist as a mixture of conformations in solution.

^{3}H-Spiroperidol binding. The pellet was suspended in 40 volumes of salt buffer (50 nM Tris-HCl, 1 nM EDTA, 50 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$, 4 mM $MgCl_2$, pH 7.2) and kept on ice until use. Triplicate determinations were conducted in borosilicate glass tubes. Each tube (final volume 1 ml) included 100 μl of 10 nM ^{3}H-spiroperidol (20 Ci/mmol, New England Nuclear), and the competitor drug (50–100 μl), both in Tris-salt buffer. Nonspecific binding was defined using 1 μM (+)-butaclamol (Ayerst) in buffer.

The reaction was initiated by the addition of 100 μl of the membrane suspension (1.5–2 mg/tube) and incubation at 37° for 30 min. Bound ligand was separated from free by rapid vacuum filtration over GF/B

TABLE 1
Atomic coordinates of 1S,2S-AJ-116·HCl

Atom	x	y	z
Cl	−0.4802 (2)	0.5000 (–)	−0.1784 (2)
N1	−0.3289 (6)	0.5123 (8)	0.1610 (6)
O1	0.1619 (7)	0.0604 (7)	0.2130 (7)
C1	0.1114 (11)	0.3749 (11)	0.4874 (10)
C2	0.2576 (11)	0.3213 (11)	0.4995 (12)
C3	0.2766 (11)	0.2179 (11)	0.4057 (10)
C4	0.1473 (10)	0.1630 (10)	0.3039 (10)
C5	0.0022 (9)	0.2132 (9)	0.2912 (10)
C6	−0.0151 (10)	0.3197 (9)	0.3829 (9)
C7	−0.1746 (11)	0.3685 (10)	0.3730 (9)
C8	−0.2821 (10)	0.3669 (9)	0.2174 (9)
C9	−0.2274 (12)	0.2906 (11)	0.1039 (10)
C10	−0.1328 (10)	0.1653 (9)	0.1744 (11)
C11	−0.1928 (10)	0.6065 (10)	0.1758 (11)
C12	−0.2322 (13)	0.7325 (12)	0.0854 (14)
C13	−0.0872 (13)	0.8027 (12)	0.0846 (18)
C14	−0.4437 (10)	0.5724 (10)	0.2277 (10)
C15	−0.5990 (9)	0.5061 (14)	0.1748 (10)
C16	−0.7076 (14)	0.5836 (17)	0.2432 (15)
C17	−0.2395 (14)	0.2801 (13)	0.4730 (12)

TABLE 2
Atomic coordinates of 1S,2R-UH-242·HBr

Atom	x	y	z
Br1	0.6118 (1)	0.8387 (–)	0.9455 (1)
Br2	0.1148 (1)	0.9999 (2)	0.4497 (1)
N1	1.2877 (7)	0.7093 (12)	0.9987 (6)
O1	0.8289 (6)	0.6615 (10)	0.9842 (6)
C1	0.9200 (10)	0.6648 (19)	0.7819 (8)
C2	0.8168 (10)	0.6689 (17)	0.7657 (9)
C3	0.7858 (9)	0.6674 (17)	0.8314 (8)
C4	0.8557 (9)	0.6639 (16)	0.9162 (8)
C5	0.9632 (8)	0.6533 (14)	0.9343 (7)
C6	0.9940 (8)	0.6562 (13)	0.8676 (7)
C7	1.1074 (9)	0.6483 (16)	0.8843 (7)
C8	1.1719 (8)	0.7119 (15)	0.9743 (8)
C9	1.1482 (9)	0.6177 (16)	1.0417 (7)
C10	1.0370 (8)	0.6543 (18)	1.0297 (7)
C11	1.3451 (10)	0.8145 (18)	1.0801 (8)
C12	1.4595 (11)	0.8248 (23)	1.1127 (11)
C13	1.5039 (13)	0.9176 (23)	1.1949 (12)
C14	1.3177 (10)	0.7564 (19)	0.9254 (8)
C15	1.2959 (12)	0.9406 (20)	0.8966 (10)
C16	1.3221 (14)	0.9735 (35)	0.8202 (13)
C17	1.1309 (11)	0.4599 (17)	0.8647 (8)
N1′	1.1796 (7)	0.5921 (13)	1.4526 (6)
O1′	1.6639 (7)	0.6421 (12)	1.5243 (6)
C1′	1.4130 (10)	0.5271 (18)	1.2983 (8)
C2′	1.5088 (10)	0.5215 (18)	1.2988 (9)
C3′	1.5943 (11)	0.5643 (18)	1.3737 (10)
C4′	1.5816 (10)	0.6074 (14)	1.4487 (8)
C5′	1.4835 (10)	0.6170 (14)	1.4488 (8)
C6′	1.3993 (10)	0.5753 (15)	1.3723 (8)
C7′	1.2893 (9)	0.5914 (14)	1.3660 (8)
C8′	1.2885 (9)	0.5716 (14)	1.4572 (8)
C9′	1.3625 (9)	0.6918 (17)	1.5192 (8)
C10′	1.4735 (10)	0.6522 (17)	1.5320 (8)
C11′	1.1722 (10)	0.5950 (17)	1.5371 (9)
C12′	1.2133 (11)	0.4357 (18)	1.5930 (10)
C13′	1.2025 (12)	0.4522 (24)	1.6808 (10)
C14′	1.1054 (10)	0.4672 (20)	1.3911 (9)
C15′	0.9941 (17)	0.4968 (46)	1.3724 (17)
C16′	0.9426 (26)	0.6274 (58)	1.3151 (33)
C17′	1.2387 (13)	0.7570 (18)	1.3168 (10)

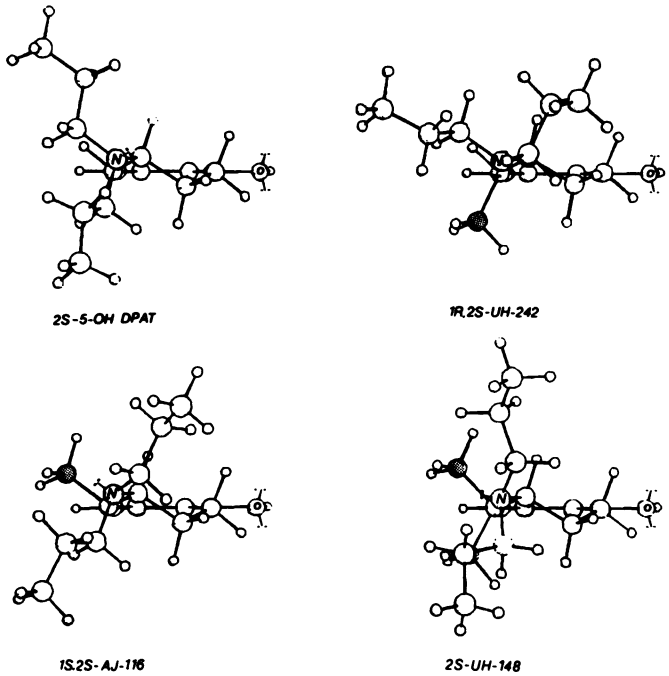


Fig. 6. Calculated (MMP2) minimum energy conformations of 2S-5-OH DPAT, 1R,2S-UH-242, 1S,2S,-AJ-116, and 2S-UH-148. Derived minimum energy conformations were calculated according to the strategy described in Ref. 19. The conformations are projected so that the *y* and *x* axes are in the plane of the paper and the non-aromatic ring is oriented toward the viewer (the coordinate system is defined in Fig. 3). For clarity, C_1-methyl groups are *shaded*. Calculated steric energies (E_s) and geometries are as follows: 2S-5-OH DPAT, E_s = 13.7 kcal/mol, $\tau_N = -176°$, $\phi = 0°$; 1R,2S-UH-242, E_s = 17.1 kcal/mol, $\tau_N = 54°$, $\phi = 15°$; 1S,2S-AJ-116, E_s = 16.8 kcal/mol, $\tau_N = -53°$, $\phi = 0°$; 2S-UH-148, E_s = 23.1 kcal/mol, $\tau_N = -24°$, $\phi = 350°$.

filters with four 3.5-ml washes of the filters with ice-cold Tris-salt buffer. The filters were placed in glass vials with 6 ml of Plasmasol (Packard). After at least 6 hr of equilibration, the vials were counted by liquid scintillation spectroscopy using a Beckman LS 1800 (47% efficacy).

^{3}H-NPA binding. This assay (^{3}H-NPA, 55.8 Ci/mmol; New England Nuclear) was performed essentially as described above for the ^{3}H-spiroperidol binding. The buffer used was a 50 mM Tris-HCl buffer with 1 mM EDTA, 4 mM $MgCl_2$, and 0.01% ascorbic acid (pH 7.2). In the assay, each tube (1 ml final volume) included 100 μl of 5 nM radioligand, 50–100 μl of the competitor drug, and 100 μl of membrane preparation (1.5–2 mg/tube), all dissolved in buffer. Nonspecific binding was defined using 10 μM (+)-butaclamol, and the incubation was performed at 25° for 30 min, followed by vacuum filtration and scintillation counting as described above.

Results

Conformational Analysis

^{1}H NMR spectroscopy. Selected ^{1}H NMR data of 5-OH DPAT·HCl, AJ-116·HCl, UH-242·HCl, and UH-148·HCl are shown in Fig. 4. Observed vicinal coupling constants in the spectra of 5-OH DPAT·HCl, UH-242·HCl, and UH-148·HCl indicate that these compounds preferentially assume half chair conformations with pseudoequatorial dipropylammonium substituents in methanol-d_4: the presence of large (dipseudoaxial) vicinal coupling constants in multiplets due to the C_2-hydrogens establish these as peseudoaxial and, thus, the dipropylammonium groups as pseudoequatorial. The presence of large coupling constants between C_3- and C_4-hydrogens, in addition to those

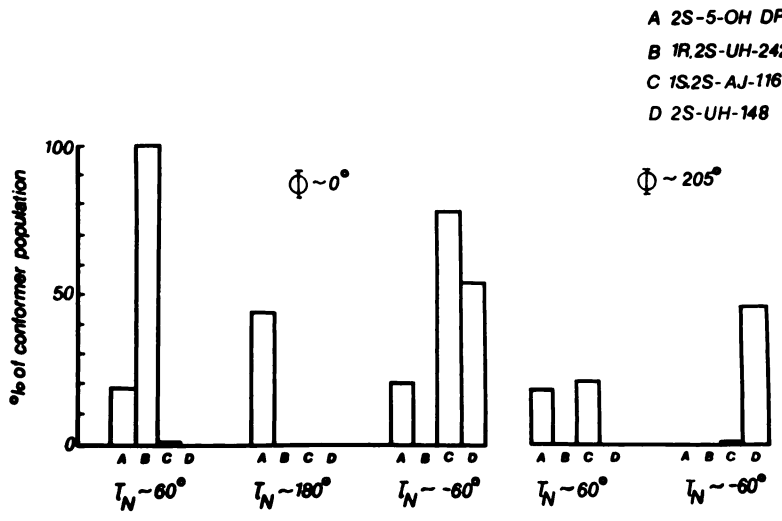


Fig. 7. Conformational distribution of 2*S*-5-OH DPAT (*A*), 1*R*,2*S*-UH-242 (*B*), 1*S*,2*S*-AJ-116 (*C*), and 2*S*-UH-148 (*D*). The probability of existence of each conformation (at 37°) was estimated from a Boltzmann distribution based on calculated (MMP2) steric energies. The *bars* represent the three staggered rotamers of the dipropylammonium group (having τ_N values around 60°, 180°, and −60°, respectively). Only conformations with ϕ values around 0° and 205° seem to be populated. Variations in ϕ values (from 0° and 205°) are as follows: 2*S*-5-OH DPAT, ±16°; 1*R*,2*S*-UH-242, ±16°; 1*S*,2*S*-AJ-116, ±60° (if the odd conformation shown in Fig. 15b is excluded, the variation is ±15°); 2*S*-UH-148, ±33°. The calculated τ_N values deviate somewhat from ideal staggered amino group rotamers. τ_N values in conformations of 2*S*-UH-148 show considerable variations; in rotamers with τ_N values around −60° and ϕ values around 0°, the calculated τ_N values range from −30° to −15°.

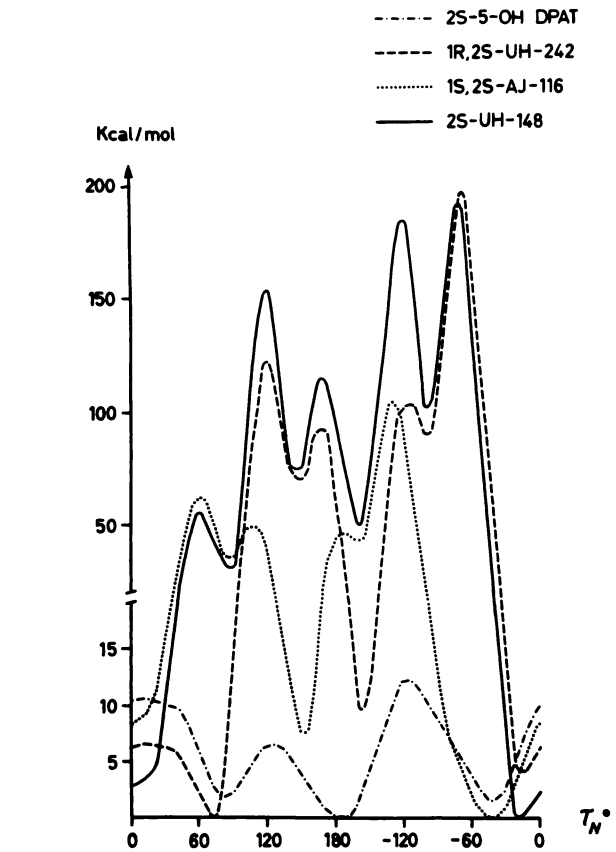


Fig. 8. Potential energy curves for rotation around the C_2-N bonds in conformations of dimethylamino derivatives of 2*S*-5-OH DPAT, 1*R*,2*S*-UH-242, 1*S*,2*S*-AJ-116, and 2*S*-UH-148 having ϕ values equal to 0°. The potential energy curves were calculated using the rigid rotation option in the MIMIC program. Rotation around the C_2-N bonds was performed using 10° increments. In this operational mode all angles are fixed except the torsion angle, which is being varied. Since no energy minimization takes place, the steric energies are considerably exaggerated. Conformations having τ_N values around 60° (a "DA D_2-receptor-agonistic τ_N value") are favored in 2*S*-5-OH DPAT and 1*R*,2*S*-UH-242. In contrast, such rotamers are disfavored in 1*S*,2*S*-AJ-116 and 2*S*-UH-148.

to the C_2-hydrogens, strongly suggests that the tetralin rings predominantly adopt half chair conformations.

No large vicinal coupling constants are present in the ^{1}H NMR spectrum of AJ-116·HCl, which thus differs considerably from spectra of the other compounds investigated here. Interestingly, also, the ^{1}H NMR spectrum of 2-amino-6,7-dimethoxy-2-methyltetralin (in $CDCl_3$) has been observed to lack large (diaxial) coupling constants (21). This appears to be due to the existence of two equally populated tetralin ring conformations (with ϕ values around 0° and 180°, respectively) in solution (19, 21). Similarly, the spectrum of AJ-116·HCl seems to reflect a time average of equilibrating tetralin ring conformations. The rather small magnitude (3.5 Hz) of the coupling constant $J_{1\alpha,2\beta}$ might, for example, be the weighted average of a very small dipseudoequatorial and a large dipseudoaxial coupling constant.

^{13}C NMR spectroscopy revealed that rotation around the C_2-N bond is slow on the NMR time scale in compounds UH-242·HCl, AJ-116·HCl, and UH-148·HCl; this was evident from the magnetic nonequivalence of C_α and C_α' (AJ-116·HCl and UH-148·HCl) and of C_β and C_β' (UH-242·HCl and UH-148·HCl). Furthermore, results from low temperature ^{13}C NMR spectroscopy of AJ-116·HCl indicate that barriers to tetralin inversion are relatively small since no line broadening of resonances due to tetralin ring carbons was apparent even at −50°. However, in low temperature ^{1}H NMR spectroscopy of AJ-116·HCl, collapse of all multiplets to broad humps occurred between 0° and −50°. This indicates that the spectrum of AJ-116·HCl at 25° reflects a rapidly interconverting (on the NMR time scale) mixture of conformations. Due to solubility problems, it was impossible to "freeze out" any conformation by recording spectra at temperatures lower than −70°.

X-Ray crystallography. Fig. 5a shows the atom numbering scheme and Tables 1 and 2 list the atomic fractional coordinates for (−)-AJ-116·HCl and (+)-UH-242·HBr, respectively.[2] The configurations of (+)-UH-242·HBr and (−)-AJ-116·HCl were determined to be 1*S*,2*R* and 1*S*,2*S*, respectively. The two conformations which were identified in the asymmetric unit of 1*S*,2*R*-(+)-UH-242·HBr have very similar ϕ and τ_N values (ϕ

[2] Anisotropic thermal parameters, hydrogen positional parameters, and lists of the observed and calculated structure factors are available from the authors on request.

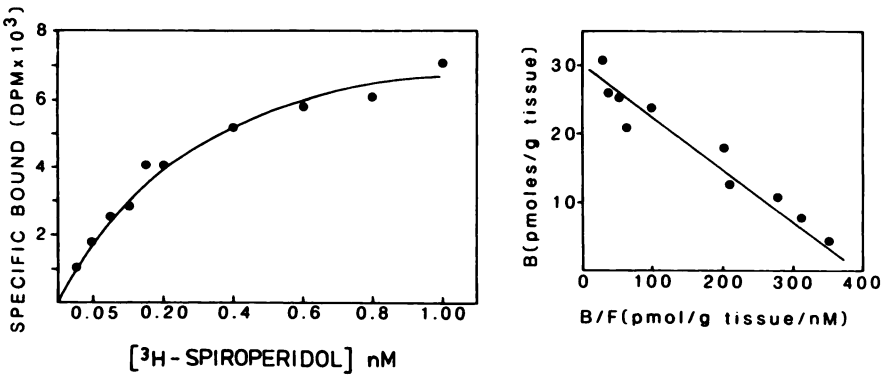


Fig. 9. Saturation of ^{3}H-spiroperidol binding in rat striatal membranes. The data points represent specific binding obtained as a function of the ^{3}H-spiroperidol concentration (0.025–1.5 nM). Specific binding was defined as binding in the presence of 1 μM (+)-butaclamol. Data points are means of three separate assays. An Eadie-Hofstee plot of data indicated a single binding with a K_D of 74 ± 3 pM and a capacity of 30.7 ± 0.47 pmol/g of tissue.

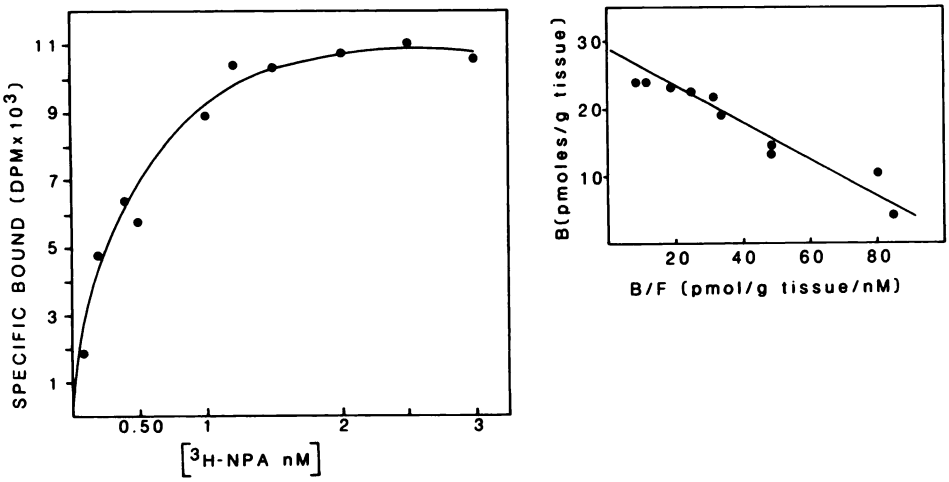


Fig. 10. Saturation of ^{3}H-NPA binding in rat striatal membranes. The data points represent specific binding obtained as a function of the ^{3}H-NPA concentration (0.1–3 nM). Specific binding was defined as binding in the presence of 1 μM (+)-butaclamol. Data points are means of three separate assays. An Eadie-Hofstee plot of data indicated a single binding with a K_D of 0.25 ± 0.025 nM and a capacity of 27.9 ± 1.2 pmol/g of tissue.

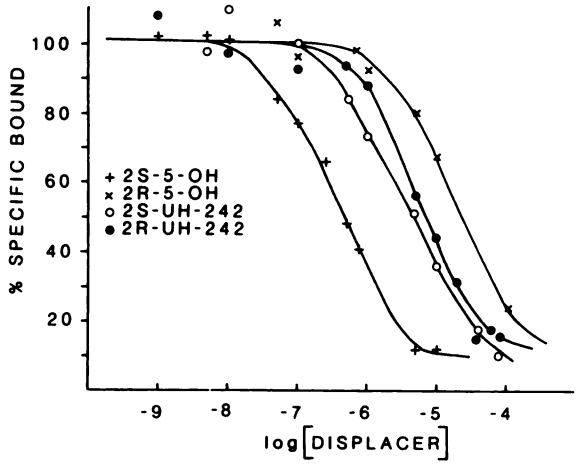


Fig. 11. Competition between ^{3}H-spiroperidol and 2-aminotetralin derivatives at DA D_2-receptors in rat striatal membranes. Binding of 1 nM ^{3}H-spiroperidol was measured at various concentrations of the indicated compound. The *curves* are based on two to three experiments, each *point* determined in triplicate.

≈ 180° and $\tau_N \approx -60°$; Fig. 5, b and c) and differ mainly with respect to conformations of the *N*-*n*-propyl groups. Only one conformation of 1*S*,2*S*-(−)-AJ-116·HCl was present in the solid state. In this conformation $\phi = 290°$ and $\tau_N = 168°$ (Fig. 5d). Apparently, the peri interactions between a pseudoequatorial C_1-methyl substituent and the C_8-hydrogen destabilize conformations with ϕ values around 0°.

Molecular mechanics calculations. The 2-aminotetralin derivatives studied herein possess a considerable amount of conformational flexibility. This is reflected in the present identification of many conformations with energies less than 2.5 kcal/mol above the respective global minimum; 17 for 2*S*-5-OH DPAT, 4 for 1*R*,2*S*-UH-242, 12 for 1*S*,2*S*-AJ-116, and 11 for 2*S*-UH-148. Fig. 6 shows computer-generated conformations which correspond to the respective global energy minimum.[3]

In general, the identified low energy conformations have ϕ values around 0° or 205°, that is, boat conformations do not appear to be energetically favorable in any of the compounds investigated. Based on the calculated steric energies of the various conformations, a Boltzmann distribution was estimated (Fig. 7); 2*S*-5-OH DPAT is able to attain any of the three possible staggered 2-dipropylamino group rotamers in tetralin conformations with ϕ values around 0°, whereas in 1*R*,2*S*-UH-242, only conformations with τ_N values around 60° appear to be energetically favorable. In 1*S*,2*S*-AJ-116 and in 2*S*-UH-148, rotamers with τ_N values around 60° are energetically disfavored in conformations with ϕ values around 0°; τ_N values from −15° to −53° appear to be favored in these conformations. The respective preferences for one of the three staggered dipropylamino rotamers in tetralin conformations with $\phi = 0°$ was also demonstrated by sequential rotation around the C_2-N bond by use of the rigid rotation option in the MIMIC program. In conformations with $\phi = 0°$, each of the four compounds investigated has a clear preference for one of the τ_N-rotamers (Fig. 8).

Results from the NMR spectroscopic investigation of the

[3] Complete lists of identified low energy conformations and steric energies are available from the authors on request.

TABLE 3

5-Hydroxy-2-(di-*n*-propylamino)tetralin derivatives: Affinities for striatal ^{3}H-spiroperidol and ^{3}H-NPA-binding sites *in vitro* and effects on rat brain *in vivo* DOPA accumulation in reserpinized rats

Competition for ^{3}H-spiroperidol and ^{3}H-NPA binding by the compounds in homogenates of rat striatal tissue is shown. IC_{50} values are expressed as the negative log of the mean; values of pIC_{50} and the Hill coefficient (n_H) are means ± standard error for *n* experiments. Also shown are previously defined doses (ED_{50} values) giving a half-maximal decrease of the dopamine synthesis rate in the striatal brain parts of reserpinized rats (4–6, 8).

Compound	^{3}H-Spiroperidol			^{3}H-NPA			ED_{50}	Ref.
	pIC_{50}	n_H	*n*	pIC_{50}	n_H	*n*		
							nmol/kg	
2*S*-5-OH DPAT	6.24 ± 0.1	0.69 ± 0.12	2	8.24 ± 0.03	0.62 ± 0.19	2	3.7	8
2*R*-5-OH DPAT	4.15 ± 0.28	0.50 ± 0.05	2	6.80 ± 0.20	0.65 ± 0.17	3	530	8
1*S*,2*S*-AJ-116	<1		2	5.79 ± 0.07	0.70 ± 0.01	2	8,700	6
1*R*,2*R*-AJ-116	<1		2	4.28 ± 0.12	0.87 ± 0.17	2	>54,000	6
1*R*,2*S*-UH-242	5.42 ± 0.33	0.58 ± 0.19	3	7.53 ± 0.56	0.75 ± 0.09	2	340	5
1*S*,2*R*-UH-242	5.15 ± 0.04	0.79 ± 0.15	3	6.56 ± 0.14	0.81 ± 0.15	3	>54,000	5
(±)-UH-148	<1		2	6.11 ± 0.02	0.70 ± 0.10	2	>50,000	4

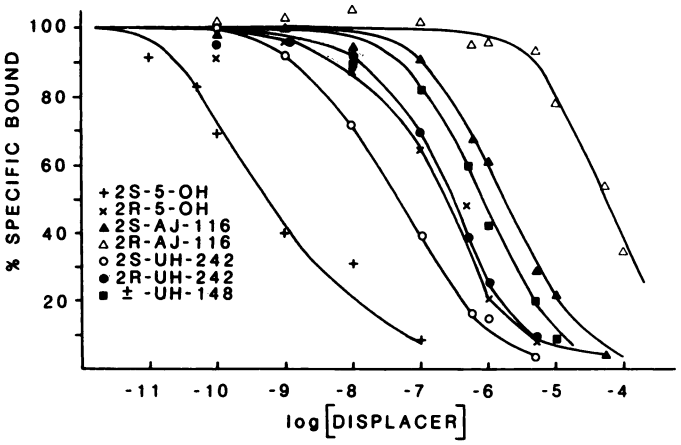


Fig. 12. Competition between ^{3}H-NPA and 2-aminotetralin derivatives at DA D_2-receptors in rat striatal membranes. Binding of 0.5 nM ^{3}H-NPA was measured at various concentrations of the indicated compounds. The *curves* are based on two to three experiments, each *point* determined in triplicate.

hydrochloride salts of 5-OH DPAT, UH-242, and UH-148 support results obtained by molecular mechanics calculations on the corresponding free bases. However, the MMP2 calculations may slightly underestimate the peri interactions between the C_8-hydrogen and the pseudoequatorial C_1-methyl group of 1*S*,2*S*-AJ-116 in conformations with ϕ values around 0°. According to the calculations (Fig. 7), conformations with ϕ values around 0° should predominate, whereas the ^{1}H NMR data appear to indicate an approximately equal preference for conformations with ϕ values around 0° and 180°. The solid state conformations of 2*R*-5-OH DPAT·HCl (9) and of 1*S*,2*R*-UH-242·HBr, which have been determined by X-ray crystallography, were identified as low energy conformations in the molecular mechanics calculations, but the solid state conformation of 1*S*,2*S*-AJ-116·HCl was found to have a steric energy 3.2 kcal/mol above that of the minimum energy conformation. However, taken together, the present and previous (19) results indicate that our calculations are of good quality.

^{3}H-Spiroperidol and ^{3}H-NPA binding. The *in vitro* binding of the 2-aminotetralin derivatives to striatal DA D_2 receptors was evaluated in competition experiments with the DA antagonist ^{3}H-spiroperidol and the DA agonist ^{3}H-NPA.

^{3}H-Spiroperidol has been used extensively to study DA D_2-receptors (22). Competition experiments have demonstrated that spiroperidol binds to more than one class of receptor sites. Approximately 80% of the binding occurs to dopaminergic sites and the remaining 20% to serotonergic sites. The dopaminergic sties are defined as D_2-receptors and consist of a homogeneous population, exhibiting more complex interactions with agonists than with antagonists. Antagonist binding is monophasic, whereas agonist binding is biphasic. This has been interpreted in terms of different affinity states for agonists. These D_2^{high} and D_2^{low} affinity states have been reported to be interconvertible and to be affected by NaCl and guanine nucleotides (23). Due to differences in experimental conditions, different values of dissociation constants of ^{3}H-spiroperidol to rat striatal membranes (0.06–1.5 nM), with varying Hill coefficients and nonlinearity of Scatchard plots, are found in the literature (24–27). To analyze ^{3}H-spiroperidol/agonist competition curves it was therefore essential to determine the dissociation constant of the radioligand under the experimental conditions used in the present study. Thus, saturation experiments of ^{3}H-spiroperidol binding were performed and the results were analyzed as Eadie-Hofstee plots (28). All plots were linear, indicating that ^{3}H-spiroperidol had equal affinity for the D_2^{high} and D_2^{low} states of the receptor. The obtained value of the dissociation constant was 74 pM and the B_{max} was 30.7 pmol/g of tissue (Fig. 9). According to the work of Grigoriadis and Seeman (23), a conversion of the high affinity state to the low affinity state for agonist interaction takes place from 45% to 15% high affinity sites under the conditions used for the ^{3}H-spiroperidol binding (a buffer containing 120 nM NaCl). Thus, the IC_{50} values obtained from the competition experiments can be considered to be related mainly to the dissociation constant for the low affinity D_2 site (K_L).

In contrast to the literature on spiroperidol binding, little data is available on DA agonist binding. In the present study, the potent DA agonist ^{3}H-NPA was used to label selectively the high affinity state of the D_2-receptor (29). Eadie-Hofstee analysis revealed a dissociation constant of 0.25 nM and a B_{max} of 27.9 pmol/g of tissue with a Hill coefficient of 0.94, indicating a homogeneous population of ^{3}H-NPA-binding sites (Fig. 10).

Only four of the 2-aminotetralin derivatives had any activity in the competition experiments with ^{3}H-spiroperidol (Fig. 11, Table 3). The Hill coefficient ranged from 0.52 to 0.73, indicating that the compounds might be competing for several sites labeled by the antagonist spiroperidol.

All seven 2-aminotetralins had appreciable affinity for the ^{3}H-NPA sites (Fig. 12, Table 3). Although the compounds gave less shallow displacement curves with ^{3}H-NPA than with ^{3}H-

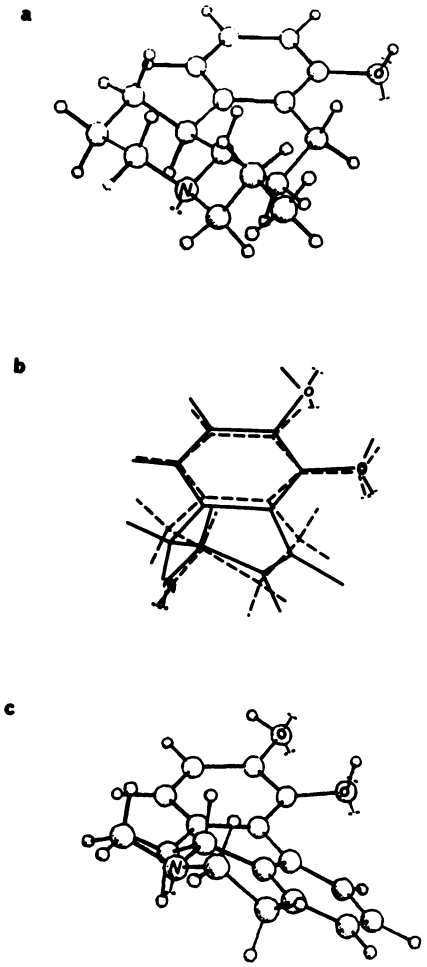


Fig. 13. Computer-generated best fit (b) of the 2-aminotetralin fragments of the minimum energy (MMP2) conformations of 6a*R*-APO (c) and 4a*S*,10b*S*-*trans*-OHBQ (a) which indicates that the "DA D_2-receptor agonistic 2-aminotetralin conformation" has a ϕ value around 0° and a τ_N value around 60°. b shows the computer-generated best fit of C_{4a}, C_5, C_6, C_7, C_8, C_{8a}, C_5-O, N, and N-electron pair in the 5-hydroxy-2-aminotetralin fragments of 6a*R*-APO (c) and 4a*S*,10b*S*-*trans*-OHBQ (a), respectively. Mean distance between fitted atoms is 0.15 Å. Three additional conformational energy minima (having steric energies 0.8, 3.0, and 3.3 kcal/mol above that of the conformation shown in a were identified in 6a*R*-APO. Only the catechol conformation shown in a was considered in the calculations since the force field is unable to accurately treat hydrogen bonds. The lowest energy conformation of 4a*S*,10b*S*-*trans*-OHBQ was identified by first minimizing various starting geometries of the tricyclic ring system and then minimizing staggered geometries of the *n*-propyl group which was added to the ring conformation being lowest in energy (the conformation with both non-aromatic rings in half chair conformations). Calculated minimum steric energies are as follows: 6a*R*-APO (c), E_s = 5.7 kcal/mol, τ_N = 52°, ϕ = 53°; 4a*S*,10b*S*-*trans*-OHBQ (a), E_s = 15.2 kcal/mol, τ_N = 55°, ϕ = 0°.

spiroperidol, the Hill coefficients were still less than unity (0.72–0.88). This might reflect an intermediate mixed agonist/antagonist character of the compounds or a binding of ^{3}H-NPA to more than one site (22).

There is still an ongoing discussion about binding to multiple sites and/or states of DA receptors (30, 31). Considerable discrepancies are found in the ratio of the values of the dissociation constants of different agonists for low over high affinity states (K_L/K_H) and in the proportion of high and low affinity sites (31–34). At present, the pharmacological (functional) relevance of the D_2^{high} and D_2^{low} sites (states) is unknown. In our opinion, it is therefore preferable to treat the inhibition values of the compounds as average affinity constants at sites or states of the DA D_2-receptor.

For comparison, doses which give a half-maximal decrease of the DOPA accumulation in reserpinized rats (ED_{50} values) are included in Table 3 (these ED_{50} values are considered to reflect agonist activity at presynaptic DA receptors; compare Refs. 4–6). Three of the compounds in the present series, 1*R*,2*R*-AJ-116, 1*S*,2*R*-UH-242, and (±)-UH-148, were considered inactive in this biochemical *in vivo* assay (4–6).

The observed affinity of 1*S*,2*R*-UH-242 for both ^{3}H-spiroperidol and ^{3}H-NPA sites is noteworthy; this compound has previously been classified as a DA receptor antagonist with preferential action on DA autoreceptors based on results obtained in biochemical and behavioral *in vivo* assays (5, 7). Based on its inability to reduce the DOPA accumulation in reserpinized rats (Table 3), the C_1-dimethylated (±)-UH-148 was considered inactive as a DA receptor agonist (4). In the present investigation a pIC_{50} value of 6.11 for ^{3}H-NPA-labeled sites was determined with this competitor. It should be noted that DA receptor antagonists do not affect the DOPA accumulation in reserpinized rats. Three interpretations of these results are possible: (a) the functional inactivity of (±)-UH-148 was due to opposing effects of the (+)- and (−)-enantiomers (i.e., one enantiomer would be agonist and the other antagonist), (b) one enantiomer is antagonist and the other is inactive, and (c) both enantiomers are antagonists. Thus, the resolution of (±)-UH-148 into the enantiomers and a relevant pharmacological evaluation are clearly warranted.

The enantiomer of 5-OH DPAT having less affinity and lower potency is the 2*R*-antipode. The 2*S*-enantiomer is very potent *in vivo* and has a high affinity both for ^{3}H-spiroperidol- and ^{3}H-NPA-binding sites (Table 3, Figs. 11 and 12). It is therefore possible that the apparent affinity and/or potency values of 2*R*-5-OH DPAT, which are shown in Table 3, are due to a small (≤1%, compare Refs. 3 and 8) contamination of the 2*S*-enantiomer. Unfortunately, it has not yet been possible to accurately determine such small enantiomeric impurities in the 5-OH DPAT enantiomers.

Discussion

Due to the structural and pharmacological similarities between the DA antagonists 6a*S*-APO and 1*S*,2*R*-UH-242 and the DA agonists 2*S*-5-OH DPAT, 1*S*,2*S*-AJ-116, 6a*R*-APO and 4a*S*,10b*S*-*tans*-OHBQ, it is reasonable to assume that they all bind to common receptor sites. This is significant since most DA antagonists differ considerably in structure from DA and probably interact with (for example) DA D_2-receptors by binding to accessory receptor areas. Thus, the present series of compounds offers a unique opportunity to obtain information about DA D_2-receptor topography.

Both 6a*R*-Apo and 4a*S*,10b*S*-*trans*-OHBQ show high potency and stereoselectivity in their interaction with DA receptors (8, 35). It is established that 6a*R*-APO is a potent D_2-agonist but the D_2-receptor affinity of 4a*S*,10b*S*-*trans*-OHBQ has not yet been determined. However, since these two compounds have similar pharmacological profiles and since the 7,8-dihydroxy analogue of 4a*S*,10b*S*-*trans*-OHBQ is a potent D_2-receptor agonist (36), it is reasonable to assume also that the 7-hydroxy derivative is a D_2-receptor agonist.

6a*R*-APO and 4a*S*,10b*S*-*trans*-OHBQ are considerably more

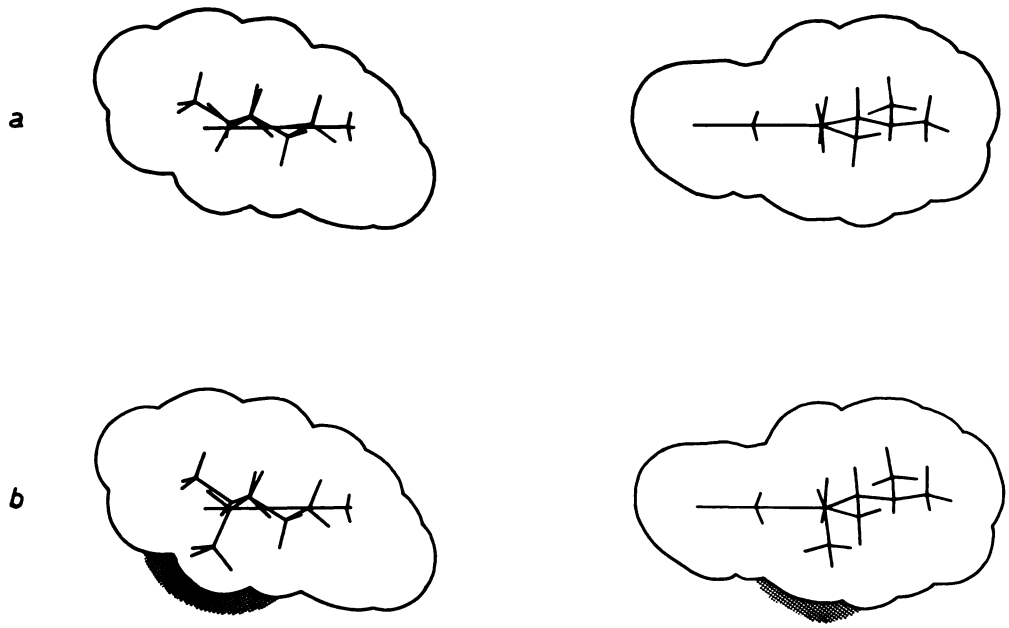


Fig. 14. Computer-aided structural comparisons of the combined van der Waals volume occupied by 6a*R*-APO and the *N*-methyl analogue of 4a*S*,10b*S*-*trans*-OHBQ (a "DA D_2-receptor-excluded volume") with the van der Waals volumes of the D_2-receptor agonists 2*S*-5-OH DPAT (a) and 1*R*,2*S*-UH-242 (b). The combined van der Waals volume of the minimum energy conformations of 6a*R*-APO (see Fig. 13c) and the *N*-methyl analogue of 4a*S*,10b*S*-*trans*-OHBQ (see Fig. 13a; for clarity, the *N*-methyl analogue was used instead of the *N*-*n*-propyl analogue) was generated from a fit of the aromatic carbons, the hydroxyl-oxygen, the nitrogen, and the N-electron pair (average distance between fitted atoms = 0.15 Å). Since the two fitted compounds are D_2-receptor agonists, with limited conformational freedom, the combined van der Waals volume should correspond to a "DA D_2-receptor-excluded volume". Two perspectives of this volume (*open areas*) are shown: to the *left* the *x* and *y* axes are in the plane of the paper and the non-aromatic ring is oriented toward the viewer; to the right the *y* axis is in the plane of the paper and the viewer looks through the *x* axis (from the negative end toward the positive). The coordinate system is defined in Fig. 3. *Solid areas* represent projections of van der Waals volumes of fitted compounds which are not encompassed by the "DA D_2-receptor-excluded volume" and which therefore may interact differently with the receptor. For clarity, fittings of 2-aminotetralins were performed with dimethylamino analogues of the minimized 2-di-*n*-propylamino derivatives. In a, the aromatic carbons, nitrogen, and the N-lone pair of electrons of the dimethylamino derivative of 2*S*-5-OH DPAT (ϕ = 344°, τ_N = 57°) are fitted with the corresponding atoms of the *N*-methyl derivative of 4a*S*,10b*S*-*trans*-OHBQ. Average distance between fitted atoms: 0.03 Å. In b, 1*R*,2*S*-UH-242 (ϕ = 0°, τ_N = 54°) is fitted similarly. Average distance between fitted atoms: 0.03 Å.

rigid than derivatives of 2-aminotetralin. Therefore, the computer-generated best fit of the 2-aminotetralin moieties of 6a*R*-APO and 4a*S*,10b*S*-*trans*-OHBQ in their lowest energy conformations (Fig. 13) is highly informative. The fit is excellent and, in fact, attempts to superimpose other conformations of the two compounds do not lead to a good fit as long as the electron pairs are included in the fitting procedure. Thus, the combined van der Waals volumes of 4a*S*,10b*S*-*trans*-OHBQ and 6a*R*-APO in their preferred conformations should correspond to a "DA D_2-receptor excluded volume" (Fig. 14) and the fitted 2-aminotetralin fragments should be in "DA D_2-receptor agonistic conformations" (see Fig. 13). These conformations have τ_N values around 60°. Similar conclusions have been reached previously by Kocjan and Hadzi (37) and by Tedesco *et al.* (11). The possible importance of the N-electron pair (N-H) orientation for DA-receptor activation has been noted by several authors (see, for example, Refs. 1 and 11). Interestingly, conformations with τ_N values around 60° and ϕ values around 0°, which are favorable for 4a*S*,10b*S*-*trans*-OHBQ, appear to be energetically disfavored in 4a*S*,10b*R*-*cis*-OHBQ, which seems to be inactive as a DA agonist (8); this compound only assumes τ_N values around −60° and 180° in low energy conformations with ϕ values around 0°.

Conformations with ϕ values around 0° and τ_N values around 60° are easily adopted by the D_2-agonists 2*S*-5-OH DPAT and 1*R*,2*S*-UH-242, but in 1*S*,2*S*-AJ-116 (and in 2*S*-UH-148) such conformations are energetically disfavored (Fig. 7). In fact, attempts to minimize geometries of 1*S*,2*S*-AJ-116 (or 2*S*-UH-148) with ϕ values around 0° and τ_N values around 60° were unsuccessful; the minimization consistently changed the tetralin ring conformation into ϕ values around 300° (Fig. 15), a conformation which is quite different from the "DA D_2-receptor agonistic 2-aminotetralin conformation." This may provide an explanation for the low *in vivo* biochemical potency and the moderate DA D_2-receptor affinity of 1*S*-2*S*-AJ-116 as compared to 4a*S*,10b*S*-*trans*-OHBQ, since the latter easily adopts a "DA D_2-agonistic 2-aminotetralin conformation" (see above), whereas the former does not.

Based on the present results, the following conclusions can be drawn. (a) The potent dopaminergic actions of 2*S*-5-OH DPAT (Table 3) are due to its ability to assume a low energy "DA D_2-agonistic conformation" without presenting a "DA D_2-receptor essential volume" (Fig. 14). (b) That the D_2 affinity of 1*R*,2*S*-UH-242 is lower than that of 2*S*-5-OH DPAT is probably due to the steric bulk of the C_1-methyl substituent which is pseudoaxially located in conformations with DA-active ϕ and τ_N values and which may have a negative influence on the receptor interaction (Fig. 14). (c) The moderate D_2 affinity of 1*S*,2*S*-AJ-116 appears to be related either to its inability to assume τ_N values around 60° in conformations with $\phi \approx 0°$, to the steric bulk of the C_1-methyl substituent and/or of the non-aromatic ring in conformations with ϕ values around 300° and τ_N values around 60° and/or to the unfavorable energies (larger than 2.4 kcal/mol above the global minimum) of such confor-

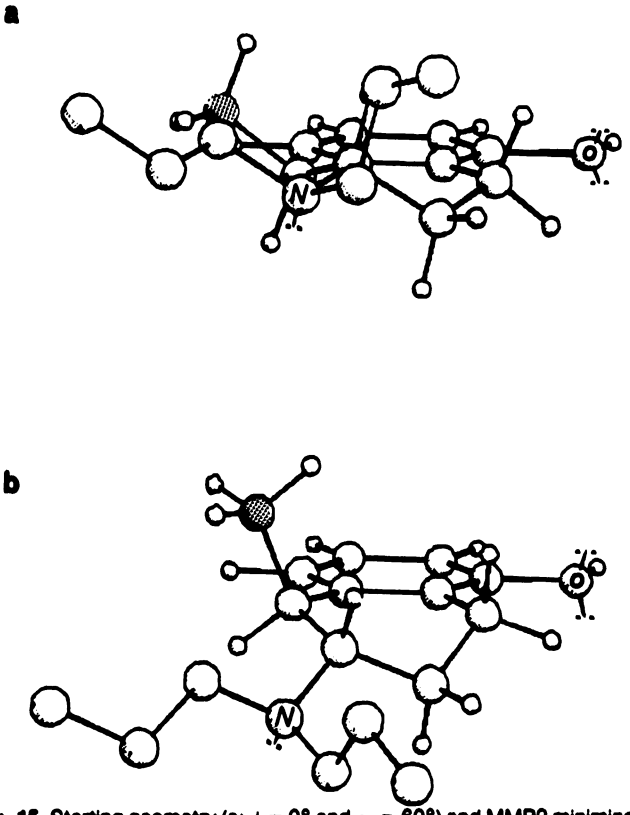


Fig. 15. Starting geometry (a; ϕ = 0° and τ_N = 60°) and MMP2 minimized conformation (b; ϕ = 300° and τ_N = 55°) of 1S,2S,-AJ-116. The conformation in b was the only one with a ϕ value close to 0° and a τ_N value close to 60° which was identified within 2.5 kcal/mol of the global minimum. Apparently, the interaction between the C_1-methyl group and $C_{a'}$ precludes the attainment of an energetically favored conformation with a ϕ value closer to 0°.

mations. (d) The inactivity of (±)-UH-148 in the biochemical *in vivo* assay and the moderate D_2-receptor affinity (Table 3) are most likely attributable to a combination of factors mentioned under conclusions b and c.

The only established DA D_2-receptor antagonist in the present series of 2-aminotetralin derivatives is 1*S*,2*R*-UH-242; it increases potently DOPA accumulation in non-pretreated rats and has a moderate affinity for D_2-receptors. 1*S*,2*R*-UH-242 appears to have a slightly lower affinity for D_2-receptors than 1*R*,2*S*-UH-242. In contrast, the affinity of 2*R*-5-OH DPAT for D_2-receptors is much lower than that of 2*S*-5-OH DPAT. 5-OH DPAT can assume any conformation which is energetically accessible for UH-242 and the only obvious structural difference between UH-242 and 5-OH DPAT is the C_1-methyl substituent. Thus, the difference in enantiomeric affinity ratios between 5-OH DPAT and UH-242 and the difference in D_2-receptor affinity between 2*S*-5-OH DPAT and 1*R*,2*S*-UH-242 can be attributed to the C_1-methyl group; the C_1-methyl substituent of 1*S*,2*R*-UH-242 does not seem to contribute unfavorably to D_2-receptor affinity, whereas that of 1*R*,2*S*-UH-242 appear to partially prevent an optimal D_2-receptor interaction.

The 2*R*-configuration of 1*S*,2*R*-UH-242 and 2*R*-5-OH DPAT makes these compounds unable to assume nitrogen electron pair orientations which, based on the structural analysis of the DA receptor agonists above, seem to be optimal for receptor interaction; this is due to the occurrence of energetically very unfavorable 1,2-diaxial interactions between the nitrogen electron pair and the C_2-hydrogen in such conformations of a 2*R*-2-aminotetralin derivative. In addition, the pseudoaxial C_3-C_4 hydrogens of the 2*R*-enantiomers may present a sterical hindrance in the receptor interaction; in half chair conformations with pseudoequatorially located amino substituents, the pseudoaxial C_2-hydrogens are located on opposite faces of the tetralin moiety in the 2*S*- and 2*R*-enantiomers, and the C_3- and C_4-hydrogens which are pseudoaxial in the 2*R*-enantiomers are pseudoequatorial in the 2*S*-enantiomers. Furthermore, in 2*S*-2-aminotetralin derivatives, the nitrogen atom is located above the plane of the aromatic ring in conformations with ϕ values around 0°, whereas the nitrogen atom is located below the plane of the aromatic ring in the corresponding conformation of the enantiomers. However, based on the present evidence, the low D_2 affinity or inactivity of 2*R*-2-aminotetralin derivatives appears to be mainly related to unfavorable τ_N values. Similarly, it is difficult to find any other common structural denominator for the D_2-antagonists 1*S*,2*R*-UH-242 and 6a*S*-APO than their inability to assume "DA D_2-receptor agonistic nitrogen electron-pair orientations." It is, however, possible that the non-hydroxylated benzene ring of 6a*S*-APO and the C_1-methyl group of 1*S*,2*R*-UH-242 contribute to DA D_2-receptor affinity by interacting favorably with portions of the D_2-receptor.

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Appendix

Geometrical Parameters[a] for Low-Energy Conformations of 2S-5-OH DPAT, 1S,2S-AJ-116, 1R,2S-UH-242, and 2S-UH-148

Conformation	ϕ (deg)	τ_N (deg)	τ_A (deg)	τ_B (deg)	$\tau_{A'}$ (deg)	$\tau_{B'}$ (deg)	Relative steric energy (kcal/mol)
			2S-5-OH DPAT				
A	344	57	61	178	−178	−170	0.5
B	344	56	60	179	179	−57	1.0
C	344	64	177	171	−63	−179	0.6
D	345	65	180	57	−63	−179	1.1
E	0[b]	−176	−52	−171	174	−170	0
F	0[b]	−177	−54	−57	173	−169	0.4
G	0[b]	−177	−53	−170	171	−54	0.2
H	0[b]	−177	−56	−56	170	−53	0.4
I	15[b]	−56	−176	170	49	170	0.4
J	15[b]	−55	−173	55	50	170	0.7
K	15[b]	−55	−176	169	52	57	0.9
L	15[b]	−53	−171	53	55	56	0.9
M	0[b]	−31	−171	172	−66	−174	2.5
N	205[b]	60	64	177	−178	−171	0.8
O	205[b]	60	64	178	179	−57	1.1
P	205[b]	66	180	170	−62	180	0.6
Q	205[b]	66	−176	56	−62	179	0.7
			1S,2S-AJ-116				
A	300[b]	55	64	−179	179	−170	2.4
B	355[b]	−53	−174	170	49	170	0
C	355[b]	−53	−171	55	50	170	0.1
D	355[b]	−53	−174	169	52	57	0.2
E	355[b]	−51	−169	53	55	56	0.1
F	345[b]	−29	−171	171	−66	−174	2.2
G	345[b]	−29	−168	55	−65	−175	2.3
H	205[b]	61	63	176	−176	−170	0.9
I	205[b]	60	63	177	180	−57	1.3
J	205[b]	66	179	170	−61	−179	0.6
K	205[b]	67	176	56	−61	179	0.8
L	205[b]	−61	176	169	53	172	2.5

Appendix—*continued*

Conformation	ϕ (deg)	τ_N (deg)	τ_A (deg)	τ_B (deg)	τ_A' (deg)	τ_B' (deg)	Relative steric energy (kcal/mol)
			1*R*,2*S*-UH-242				
A	15	54	61	180	180	−170	0
B	15	54	61	−179	177	−56	0.2
C	16	60	176	171	−63	−177	0.3
D	16	60	179	58	−63	−177	0.8
			2*S*-UH-148				
A	356	−30	−142	176	177	−172	2.1
B	350	−24	−158	173	71	173	0
C	348	−24	−163	52	71	173	0.1
D	354	−27	−157	161	77	69	0.7
E	349	−27	−161	58	76	68	0.8
F	351	−15	−169	170	−67	180	0.3
G	351	−15	−169	56	−67	180	0.4
H	213	−53	−164	170	51	170	0.1
I	213	−54	−167	54	51	170	0.3
J	212	−53	−163	170	54	57	0.3
K	213	−54	−167	53	55	57	0.4

[a] For definitions, see Ref. 19.
[b] Approximate ϕ value estimated by comparison with relevant conformations of C_2-unsubstituted tetralin.

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